



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A01K 67/027, C07K 16/00, 16/24, 16/28 // C12N 15/85, 15/90</b>		A3	(11) International Publication Number: <b>WO 98/24893</b> (43) International Publication Date: <b>11 June 1998 (11.06.98)</b>
<p>(21) International Application Number: <b>PCT/US97/23091</b></p> <p>(22) International Filing Date: <b>3 December 1997 (03.12.97)</b></p> <p>(30) Priority Data: <b>08/759,620 3 December 1996 (03.12.96) US</b></p> <p>(71) Applicant: ABGENIX, INC. [US/US]; 7601 Dumbarton Circle, Fremont, CA 94555 (US).</p> <p>(72) Inventors: JAKOBOVITS, Aya; 2021 Monterey Avenue, Menlo Park, CA 94025 (US). KUCHERLAPATI, Raju; 8 Gracie Lane, Darien, CT 06820 (US). KLAPHOLZ, Sue; 76 Peter Coutts Circle, Stanford, CA 94305 (US). MENDEZ, Michael; P.O. Box 787, El Granada, CA 94018 (US). GREEN, Larry; 70 Crestline Drive #2, San Francisco, CA 94131 (US).</p> <p>(74) Agents: HALEY, James, F., Jr. et al.; Fish &amp; Neave, 1251 Avenue of the Americas, New York, NY 10020 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published  <i>With international search report.</i>  <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report: <b>20 August 1998 (20.08.98)</b></p>	

**24**

(54) Title: TRANSGENIC MAMMALS HAVING HUMAN Ig LOCI INCLUDING PLURAL V<sub>H</sub> AND V<sub>K</sub> REGIONS AND ANTIBODIES PRODUCED THEREFROM

(57) Abstract

The present invention relates to transgenic non-human animals that are engineered to contain human immunoglobulin gene loci. In particular, animals in accordance with the invention possess human Ig loci that include plural variable (V<sub>H</sub> and V<sub>K</sub>) gene regions. Advantageously, the inclusion of plural variable region genes enhances the specificity and diversity of human antibodies produced by the animal. Further, the inclusion of such regions enhances and reconstitutes B-cell development in the animals, such that the animals possess abundant mature B-cells secreting extremely high affinity antibodies.

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# INTERNATIONAL SEARCH REPORT

Internal Application No  
PCT/US 97/23091

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 A01K67/027 C07K16/00 C07K16/24 C07K16/28 //C12N15/85,  
 C12N15/90

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 A01K C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>A. JAKOBIVITS ET AL., : "Production of antigen-specific human antibodies from mice engineered with human heavy and light chain YACs"  <i>ANNALS OF THE NEW YORK ACADEMY OF SCIENCES</i>,          vol. 764, 1995, NEW YORK, NY, US,          pages 525-535, XP002067728          see the whole document but specially pages 533-534</p> <p>---</p> <p style="text-align: center;">-/-</p>	1-16

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

12 June 1998

Date of mailing of the international search report

25/06/1998

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/23091

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 25585 A (GENPHARM INT ) 10 November 1994 cited in the application see page 1, line 19-33 see page 6, line 24 - page 7, line 23 see page 11, line 6 - page 12, line 19 see page 23, line 25 - page 24, line 7 see page 48, line 35 - page 49, line 22; examples 1-5 see page 185, line 26 - page 190, line 31 see page 198, line 18-30 see page 202, line 16-36 ----	1,2, 6-10,16, 24
A	WO 96 34096 A (CELL GENESYS INC) 31 October 1996 cited in the application see page 2, line 20-34 see page 13, paragraph 31-33 see page 15, line 14-21; examples 2,3 ----	1,16,17, 19-21, 23,24
A	WO 91 00906 A (GENETICS INST) 24 January 1991 see the whole document ----	1,11-16
A	L.D. TAYLOR ET AL.: "A transgenic mouse that expresses a diversity of human sequence heavy and light chain immunoglobulins" NUCLEIC ACIDS RESEARCH, vol. 20, no. 23, 1992, OXFORD, GB, pages 6287-6295, XP002041128 cited in the application see the whole document ----	1-16, 26-28
A	M. BRUGGEMAN AND N.S. NEUBERGER: "Strategies for expressing human antibody repertoires in transgenic mice" IMMUNOLOGY TODAY, vol. 17, no. 8, 1 August 1996, OXFORD, GB, pages 391-397, XP002067729 cited in the application see the whole document ----	1-28
P,X	M.J. MENDEZ: "Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice" NATURE GENETICS, vol. 15, no. 2, 1 February 1997, NEW YORK, NY, US, pages 146-156, XP002067603 see the whole document ----	1-15
		-/-

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 97/23091

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	A. JAKOBOVITS ET AL., : "Human immunity in mice engineered with megabase human heavy and kappa light chain YACs" THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, vol. 99, no. 1, part 2, 1 January 1997, SAINT LOUIS, MO, US, page S113 XP002067604 see abstract -----	1-15
P,X	J.R.F. CORVALAN ET AL., : "Generation of fully human high affinity monoclonal antibodies to EGF receptor in mice" THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, vol. 99, no. 1, part 2, 1 January 1997, SAINT LOUIS, MO, US, page s214 XP002067605 see abstract -----	1,16,18, 20,22,24
P,X	X.D. YANG ET AL.,: "Human monoclonal antibodies to human TNF-alpha generated from mice carrying human Ig loci" THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, vol. 99, no. 1, part 2, 1 January 1997, SAINT LOUIS, MO, US, page s15 XP002067606 see abstract -----	1,16,19, 20,23,24

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/US 97/23091

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		JP	8509612 T	15-10-1996
		US	5625126 A	29-04-1997
WO 9634096 A	31-10-1996	JP	8140528 A	04-06-1996
		AU	2466895 A	18-11-1996
WO 9100906 A	24-01-1991	EP	0823941 A	18-02-1998
		NONE		

PCT

特許協力条約に基づいて公開された国際出願



(51) 国際特許分類6 A01K 67/027	A1	(11) 国際公開番号 <b>WO98/37757</b>
		(43) 国際公開日 1998年9月3日(03.09.98)
(21) 国際出願番号 PCT/JP98/00860		(74) 代理人 弁理士 平木祐輔, 外(HIRAKI, Yusuke et al.) 〒105-0001 東京都港区虎ノ門一丁目17番1号 虎ノ門5森ビル3F Tokyo, (JP)
(22) 国際出願日 1998年3月2日(02.03.98)		
(30) 優先権データ 特願平9/62309 1997年2月28日(28.02.97) JP		(81) 指定国 AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO特許 (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), 欧州特許 (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI特許 (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
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〒683-8503 鳥取県米子市西町86 鳥取大学 医学部 生命科学科内 Tottori, (JP)		
(54) Title: PLURIPOTENT CELLS HAVING DISRUPTED INTRINSIC GENES		
(54) 発明の名称 内因性遺伝子が破壊されている分化多能性保持細胞		
(57) Abstract		
A process for constructing a chimeric non-human animal characterized by preparing microcells containing one or more foreign chromosomes or fragments thereof, and transferring the one or more foreign chromosomes or fragments thereof into pluripotent cells through fusion with the microcells; chimeric non-human animals which can be constructed by the above process and offspring thereof; tissues and cells originating in the above animals; methods for using the individuals, tissues and cells of the animals; pluripotent cells containing one or more foreign chromosomes or fragments thereof, a process for constructing these cells, and the use of these cells; pluripotent cells in which at least two intrinsic genes have been disrupted; a process for constructing the above cells by homologous recombination; etc.		

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/00860

A. CLASSIFICATION OF SUBJECT MATTER  
Int.Cl<sup>6</sup> A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
Int.Cl<sup>6</sup> A01K67/027

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
JICST File on Science and Technology  
BIOSIS PREVIEWS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	Nature Genetics, 16[2] (1997) p.133-143 Full text	1-40, 42, 43, 45-53 41, 44, 54-76
P, Y	Full text	
Y	JP, 05-328878, A (The Institute of Physical and Chemical Research), December 14, 1993 (14. 12. 93), Full text (Family: none)	1-76
Y	JP, 07-067629, A (K.K. Dinado), March 14, 1995 (14. 03. 95), Full text (Family: none)	1-76
Y	EMBO Journal, 2 (1983) p.1963-1968 Full text	1-76
Y	Proc. Natl. Acad. Sci. USA, 74 (1997) p.319-323 Full text	1-76

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Date of the actual completion of the international search  
May 21, 1998 (21. 05. 98)Date of mailing of the international search report  
June 2, 1998 (02. 06. 98)Name and mailing address of the ISA/  
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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP98/00860

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y A	WO, 89/05308, A1 (GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG MBH), June 15, 1989 (15. 06. 89), Full text Full text & JP, 02-502426, A	41, 44, 54, 55 1-40, 42, 43, 45-53, 56-63

国際調査報告

国際出願番号 PCT/JP98/00860

## A. 発明の属する分野の分類(国際特許分類(IPC))

Int. Cl. A01K67/027

## B. 調査を行った分野

調査を行った最小限資料(国際特許分類(IPC))

Int. Cl. A01K67/027

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース(データベースの名称、調査に使用した用語)

JICST 科学技術文献ファイル  
BIOSIS PREVIEWS

## C. 関連すると認められる文献

引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
P, X	Nature Genetics, 16[2] (1997) p. 133-143 全文	1-40, 42, 43, 45-53 41, 44, 54-76
P, Y	全文	
Y	J P, 05-328878, A (理化学研究所) 14. 12月. 1993 (14. 12. 93) 全文(ファミリーなし)	1-76

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国際調査を完了した日

21. 05. 98

国際調査報告の発送日 02.06.98

国際調査機関の名称及びあて先

日本国特許庁 (ISA/JP)

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特許庁審査官(権限のある職員)

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引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	
Y	J P, 07-067629, A (株式会社ディナード) 14. 3月. 1995 (14. 03. 95) 全文 (ファミリーなし)	1-76
Y	EMBO Journal, 2 (1983) p. 1963-1968 全文	1-76
Y	Proc. Natl. Acad. Sci. USA, 74 (1977) p. 319-323 全文	1-76
Y A	WO, 89/05308, A1 (GESELLSCHAFT FUR BIOTECHNOLOGISCHE FORSCHUNG MBH) 15. 6月. 1989 (15. 06. 89) 全文 全文 & J P, 02-502426, A	41, 44, 54, 55 1-40, 42, 43, 45-53, 56-63